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Original Article

Difficulties in the diagnosis and management of eight infants with secondary pseudohypoaldosteronism

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ABSTRACT

Background. Type 1 pseudohypoaldosteronism (PHA1) is a rare condition characterized by the resistance of the kidney to the effect of aldosterone. Secondary PHA1 is a syndrome that is most often related to urinary tract anomalies (UTAs) and/or urinary tract infections (UTIs). A similar pattern of electrolyte impairment is seen in congenital adrenal hyperplasia (CAH) and secondary PHA1, and CAH is a condition that requires urgent treatment. In our study, eight patients aged between 15 days and 8 months (seven males and one female) were included in the evaluation. It was aimed to evaluate cases of secondary PHA1 in our clinic and to identify the problems encountered in diagnosis and follow-up.

Methods. The records of the patients who presented to our hospital between February 2010 and 2021 were retrieved and retrospectively scanned.

Results. In all cases, hyponatremia, hyperkalemia, hyperaldosteronism, and hyperreninemia were detected. Other biochemical and hormonal tests were normal. Leukocytosis was detected in urine analysis, and urine cultures were productive. UTA was detected in five cases. Nine episodes of PHA1 occurred in eight patients and fungal infections were responsible for causing two episodes. Four episodes of PHA1 needed mineralocorticoid treatment. On the third day, serum electrolytes normalized. Fludrocortisone treatment was continued for 1 week. In one case, UTIs were repeated with PHA1, but in the follow-up, there were no additional problems.

Conclusions. Secondary PHA1 should be kept in mind when hyponatremia and hyperkalemia are seen, especially in infants aged under 3 months or older, up to 8 months, who present with non-specific symptoms. Fungal infections should not be forgotten in UTI etiology because PHA1 episodes can be initiated. If CAH is suspected, mineralocorticoid treatment should be rapidly initiated.

Key words: fungal urinary infection, secondary pseudohypoaldosteronism, urinary tract anomaly, urinary tract infection.

Aldosterone plays a major role in the control of blood pressure through the control of sodium balance, fluid homeostasis, and transepithelial sodium transport.[1] The main effect of aldosterone in epithelial target tissues is to regulate sodium reabsorption, and potassium and hydrogen secretion. Aldosterone regulates this pathway through intracellular mineralocorticoid receptors (MR) and amiloride-sensitive epithelial sodium channels. Interruption of the intracellular MR signal pathway leads to the appearance of clinical signs of pseudohypoaldosteronism (PHA). Type 1 PHA (PHA1) is a rare condition characterized by the resistance of the kidney to the effect of aldosterone. In patients, metabolic acidosis associated with elevated plasma renin and aldosterone levels manifests with hyperkalemia and salt loss.[2] This rare syndrome starts in the neonatal period and early infancy and has two forms; (a) Genetic forms: There are two types, the renal form (autosomal dominant) and systemic form (autosomal recessive), (b) The secondary form of PHA1 which is limited to the kidney, most often related to urinary tract anomalies (UTAs) and/or urinary tract

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infections (UTIs) and is identified in newborns and infants.[3] Secondary PHA1 is a problem that causes difficulties in diagnosis and treatment, which can be overlooked in early childhood and confronted with different causes.

A similar pattern of electrolyte impairment is seen in congenital adrenal hyperplasia (CAH) and PHA1 in infancy. CAH remains the most common cause and is a condition that requires urgent treatment.[4] The incidence of the classic form of CAH is reported to range from 1:5000 to 1:15,000 and varies among ethnic/racial backgrounds.[5] CAH is a group of autosomal recessive disorders encompassing enzyme deficiencies in the adrenal steroidogenesis pathway. Hyperpigmentation of skin creases and genitalia may be early signs of adrenal insufficiency. Depending on excessive androgen exposure, virilization findings occur in the external female genitalia; the external genitalia in males are usually unaffected, except for subtle penile enlargement. In CAH, low levels of aldosterone and cortisol, and elevated levels of renin, 17 hydroxyprogesterone (17 OHP), and adrenocorticotropic hormone (ACTH) are detected.[6] The management of secondary PHA1 involves sodium supplementation and water replacement, ion exchange resins in cases of high potassium values, in some cases bicarbonate, antibiotics for UTIs, and surgical intervention for UTA when necessary.[7] Stress-dose corticosteroids may be given to patients until the end of the hormone tests taken for differential diagnosis.[4]

In this study, it was aimed to evaluate cases of secondary PHA1 in our clinic, and to identify the problems encountered in diagnosis and follow-up.

Material and Methods

The records of the patients who presented to our hospital between February 2010 and 2021 were retrieved and retrospectively scanned. The study protocol was approved by the Institutional Ethics Committee of Ankara University (approval number: 14-675-16). Informed consent was received from the parents of all patients included in the study.

Patients

Eight patients were included who were evaluated for hyperkalemia and hyponatremia. Hyperkalemia was accepted when the potassium level was ≥5.1 milliequivalents (mEq)/Liter (L) and hyponatremia, sodium level was <136 mEq/L. The bicarbonate level for acidosis was considered as <22 mEq/L, 17 OHP, cortisol, ACTH, plasma renin activity (PRA), and aldosterone levels were measured when hyponatremia and hyperkalemia were detected. Urinary system obstructions were evaluated using urinary ultrasonography (US) and voiding cystourethrography (VCUG). UTI was considered to be above five leukocytes/high-power field (hpf) in urine analysis microscopy and urine culture with a single pathogen greater than 10^5 colonies (col)/milliliter (mL). Reproduction above 10^4 col/mL was considered significant for fungal infections. Urine samples were taken using a urine catheter. Treatment with intravenous (IV) fluid and sodium replacement, IV antibiotics and/or antifungal agents was started. It was recorded whether glucocorticoids and/or mineralocorticoids were given.

Case Presentation

The clinical features and laboratory findings of the patients are shown in Tables I and II. On initial examination, all patients had hyperkalemia (6.9±1.0 mEq/L), hyponatremia (118.5±5.5 mEq/L), hyperaldosteronism (462.5±167.4 ng/dL), and hyperreninemia (116.6±67.6 ng/mL/hr). There was no history of parental consanguinity, no signs of atypical external genitalia, or hyperpigmentation in our cases.

Patient 1 was admitted to the emergency department due to weakness and the inability to feed orally. His physical examination showed decreased skin turgor and poor peripheral

Table I. Clinical features of patients.

Patient	Sex	Age at admission	Birth weight/ week	Type of urinary malformation	Surgical treatment	Urinalysis-Urine culture on admission
1	Male	3 months	1060 g/27 week	-	-	44 leucocyte/hpf-10^5 col/mL *Klebsiella Pneumoniae*
2	Male	1.5 months	2350 g/34 week	PUV	Stenosis excision at 2.5 months, Left nephroureterectomy and right ureteronephrostomy at 9.5 months	234 leucocytes/hpf-10^5 col/mL *Candida Glabrata*
3	Male	2.5 months	2980 g/35 week	PUV	Stenosis excision at 3 months old	885 leucocytes/hpf-$8x10^4$ col/mL *Candida Albicans*
		4.5 months (2nd episode)				24 leucocytes/hpf-10^5 col/mL *Klebsiella Pneumoniae*
4	Girl	2.5 months	2990 g/40 week	Neurogenic bladder secondary to meningomyelocele	-	219 leucocytes/hpf-10^5 col/mL *Klebsiella Pneumoniae*
5	Male	6 months	3180 g/38 week	Left UP stenosis	Left pyeloplasty at 3.5 months old	213 leucocytes/hpf-10^5 col/mL *Enterobacter cloacae*
6	Male	8 months	2870 g/40 week	-	-	7 leucocytes/hpf-10^5 col/mL *Escherichia coli*
7	Male	1.5 months	2950 g/38 week	Double collecting system in the right kidney, Bilateral VUR	-	259 leucocytes/hpf-10^5 col/mL *Klebsiella Pneumoniae*
8	Male	15 days	3900 g/40 week	PUV	-	1746 leucocytes/hpf-10^5 col/mL *Enterobacter Bugadensis*

UP: ureteropelvic, PUV: posterior urethral valve, hpf: high-power field

circulation. A UTI was detected in a urine test. The patient was evaluated as having secondary PHA1 due to UTI. Hydrocortisone (single-dose) and fludrocortisone were added to antibiotic and IV sodium replacement therapy for possible surrenal insufficiency. Fludrocortisone was discontinued at the end of the first week when the 17 OHP result was normal.

Patient 2 presented with vomiting. His clinical examination showed dehydration. Antenatal US had shown bilateral hydronephrosis (HN). His laboratory findings suggested PHA1 secondary to UTI and UTA. He was treated first with IV saline. The IV fluconazole treatment was completed in 3 weeks.

Patient 3 was admitted with vomiting and irritability. Physical examination showed dehydration. Bilateral HN had been detected at the 31st week of gestation. On postnatal day 5, the patient was diagnosed as having a posterior urethral valve (PUV). At admission, he was considered to have secondary PHA1 associated with UTI and UTA. IV sodium replacement treatment for hyponatremia was started. IV fluconazole treatment was continued for 2 weeks. After the PUV resection surgery, when

Table II. Laboratory features of the patients on admission and clinical follow-up.

Patients	BUN	Cr	Na	K	Cl	pH	HCO3	PRA	Aldosterone	ACTH	Cortisol	17 OHP	Treatment
Patient 1	15	0.09	123	6	100	7.30	17	277.6	552	7.5	25.52	1.63	IV antibiotic, IV fluid, Hydrocortisone (single-dose), Fludrocortisone (1 wk)
Day 3			136	4.1									
Day 14								1.27	0.81	50.01	6.6		
Day 21								1.8	17				
Patient 2	41	0.40	112	7.7	102	7.28	12.5	121.6	551	50.80	39.52	2.65	IV antibiotic + antifungal, IV fluid
Day 3	13	0.50	137	4.3	102								
Day 14								0.9	15.1				
Patient 3 1st PHA episode	52	0.66	115	8.1	105	7.27	13.2	97.7	242	11.36	31.69	1.89	IV antifungal, IV fluid
Day 3	3	0.34	137	5									
Day 14								1.1	16	45.05	7.5		
2nd PHA episode (2 mths later)	12	0.55	123	6.8				97.7	480	5.07	30.81		IV antibiotic, IV fluid
Day 2			138	4.9									
Day 14								30.6	187.9				
Day 28								1.9	17				
Patient 4	8	0.18	128	5.2	99	7.33	18	143.8	497.8	7.7	7.71	2.33	IV antibiotic, IV fluid
Day 3			136	4.2									
Day 21								0.92	15.5				
Patient 5	23	0.42	119	6.2	101	7.28	13	105	390	22.86	6.25	2.55	IV antibiotic, IV fluid
Day 2	2	0.17	138	5.1									
Day 14								1.2	14.5				
Patient 6	6	0.24	119	7.2	104	7.36	20.6	86.3	300	7.9	60.60	1	IV antibiotic, IV fluid, Hydrocortisone (single-dose), Fludrocortisone (1 wk)
Day 3			136	4									
Day 7								0.51	5.93				

Normal Laboratory Values: BUN: 5-18 mg/dl, Creatinin (Cr): 0.32-0.6 mg/dl, Sodium (Na): 136-145 mEq/L, Potassium (K): 3.5-5.1 mEq/L, Clor (Cl): 98-108 mEq/L, Bicarbonate (HCO3): 22-26 mEq/L, Plasma Renin Activity (PRA): 0.5-1.9 ng/mL/hr, Aldosterone: 0.8-17.2 ng/dL, Adrenocorticotropic hormone (ACTH): 7.2-63.3 pg/mL, Cortisol: <10 mcg/dL, 17 hydroxyprogesterone (17 OHP): <3 ng/mL

Table II. Continued.

Patients	BUN	Cr	Na	K	Cl	pH	HCO3	PRA	Aldosterone	ACTH	Cortisol	17 OHP	Treatment
Patient 7	90	1.16	111	7.6	105	7.04	5.2	30	350	10.60	24.92	2.89	IV antibiotic, IV fluid, Hydrocortisone (single-dose), Fludrocortisone (1 wk)
Day 3	17	0.49	136	4.3									
Day 7								1.72	4.6				
Patient 8	40	0.56	117	8.1	99	7.27	12.6	90	800	7.5	25.9	2.5	IV antibiotic, IV fluid, Hydrocortisone (single-dose), Fludrocortisone (1 wk)
Day 3	16	0.40	137	4.2									
Day 28								1.8	53				

Normal Laboratory Values: BUN: 5-18 mg/dl, Creatinin (Cr): 0.32-0.6 mg/dl, Sodium (Na): 136-145 mEq/L, Potassium (K): 3.5-5.1 mEq/L, Clor (Cl): 98-108 mEq/L, Bicarbonate (HCO3): 22-26 mEq/L, Plasma Renin Activity (PRA): 0.5-1.9 ng/mL/hr, Aldosterone: 0.8-17.2 ng/dL, Adrenocorticotropic hormone (ACTH): 7.2-63.3 pg/mL, Cortisol: <10 mcg/dL, 17 hydroxyprogesterone (17 OHP): <3 ng/mL

he was aged 4.5 months, he underwent a second PHA1 episode after a UTI.

Patient 4 presented for evaluation routinely. Her history was characterized by the presence of meningomyelocele and flaccid paralysis of the lower extremities. Clean intermittent catheterization was performed since the 2nd month. Physical examination showed a meningomyelocele sac in the sacral region. She was accepted as having PHA1 due to UTI.

Patient 5 presented with vomiting. The physical examination was normal. Dilatation of the left renal collecting system had been detected during the antenatal period. Previous imaging studies revealed grade 4 ectasia and ureteropelvic (UP) stenosis on the left kidney using US. He was considered as having secondary PHA1 caused by obstructive uropathy and UTI.

Patient 6 was admitted to the emergency department due to lethargy and decreased oral acceptance. His physical examination showed dehydration and circulatory collapse. A urine microscopy examination revealed UTI. He was accepted as having PHA1 due to UTI. Corticosteroids were added to the therapy for possible surrenal insufficiency. Fludrocortisone was discontinued at the end of the first week.

Patient 7 presented with vomiting and oral intolerance. He had dehydration and pallor and did not look well. In his abdominal US, a double collecting system was detected on the right kidney and grade 2 dilatation on the left kidney. Bilateral grade 5 vesicoureteral reflux (VUR) was observed in VCUG. UTI was detected in a urine test. He was considered to have secondary PHA1 caused by UTA and UTI. Hydrocortisone (single-dose) and fludrocortisone were started. CAH was excluded when the 17 OHP level was normal.

Patient 8 presented to the emergency department with a one-week history of poor feeding, vomiting, and lethargy. Urine microscopic examination revealed UTI. Antenatal US had shown bilateral HN and PUV was detected in the postnatal period. He was accepted as having

PHA1 due to UTI and UTA. Corticosteroids were added to the therapy. Mineralocorticoid therapy was discontinued at the end of the first week.

Among our patients, males were in the majority (87.5%, 7/8) and 62.5% (5/8) were in the under 3 months age group. Although UTI was present in eight of our patients, there was no underlying UTA in two of these patients; one patient had a neurogenic bladder secondary to meningomyelocele. UTA and UTI were observed in 62.5% (5/8) of our patients. All patients recovered from their electrolyte imbalances on the third day of hospitalization with antibiotic and/or antifungal treatment for underlying infections and intravenous saline. Hydrocortisone (single-dose) and fludrocortisone were added to the therapy for possible surrenal insufficiency in *Patient 1*, *Patient 6*, *Patient 7*, and *Patient 8*.

Discussion

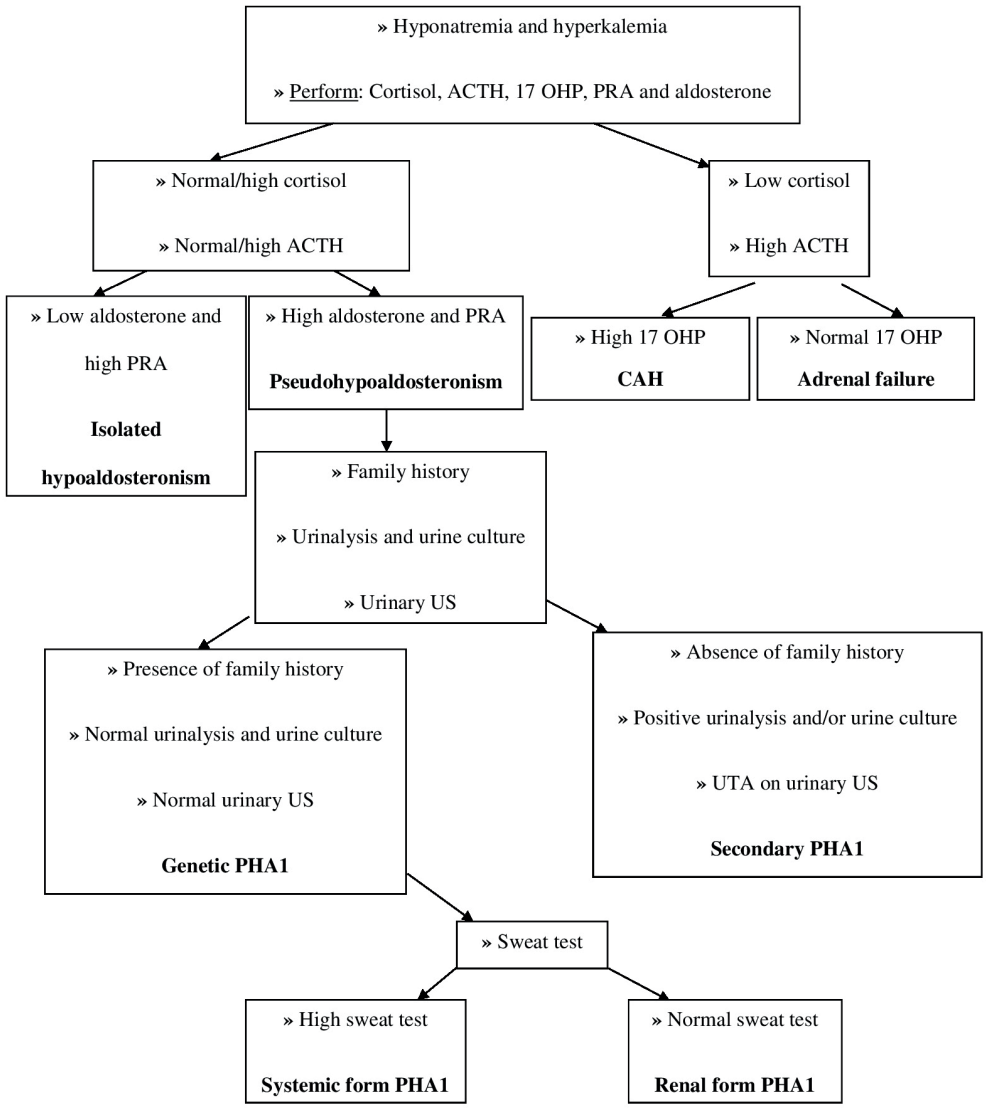
Secondary PHA1 is due to transient aldosterone resistance and has been described in infants with urinary tract malformations or UTIs or both.[8] Searching MEDLINE, we found 137 cases of transient PHA1 since 1983.[4,9-20] Most of the reported cases by sex were male 70.5% (91/129, 1:1.41), and 84.6% (116/137, 1:1.18) were in the under 3 months age group. In our study, male sex was more prevalent, on the other hand, the age group under 3 months was found to be lower than in the literature.

In the literature, UTA was present in 125 of 137 patients (91.1%), UTA and UTI were seen together in 87.2% (109/125) of cases.[4,9-20] UTA and UTI were observed in 62.5% of our cases. Uncircumcised male infants aged under 3 months have the highest baseline prevalence of UTI and the incidence of obstructive uropathy is higher in males than females.[21] The risk of severe electrolyte imbalance in children with obstructive uropathy is significantly reduced after 3 months and this age-related condition seems to be related to immaturity in kidney tubules.[22] We believe that the frequency of PHA1 is higher in boys aged under 3 months for these reasons. Although the true prevalence of PHA1 associated with UTI and/or UTA is not known, it may be higher than reflected in the published literature because ascertainment is dependent on physician awareness.

The underlying pathogenesis of secondary PHA1 is unclear. Possible mechanisms include the emergence of bacterial endotoxin damage at the aldosterone receptors secondary to cytokines such as transforming growth factor-β (TGF-β), and parenchymal scarring secondary to obstruction.[23] Urinary tract obstruction increases the intrarenal synthesis of many cytokines, such as interleukin (IL)-1, IL-6, tumor growth factor (TGF)-β1, and tumor necrosis factor alfa (TNF-α).[24] TGF-β1 is produced from infiltrated macrophages and renal tubule cells and suppresses the effect of aldosterone by reducing MR susceptibility.[25]

Severe hyponatremia, hyperkalemia, and dehydration may be seen with CAH, isolated aldosterone deficiency, and other forms of hypoadrenalism, or PHA.[9] The most common cause of hypoaldosteronism is adrenal failure, which is usually caused by CAH during early life. Treatment should begin as soon as possible for the possibility of adrenal insufficiency. If CAH is excluded, hydrocortisone is stopped.[4] In cases of hyponatremia and hyperkalemia, the key finding of elevated serum aldosterone and renin level strongly suggests the diagnosis of PHA1.[9] Two forms of PHA1 can be distinguished at the clinical and genetic level. Family history, laboratory studies, and the presence of urinary tract malformations and/or UTI may help to differentiate genetic PHA1 from secondary PHA1. The sweat test helps when considering the genetic form; if the sweat test result is normal, the renal form should be considered, and if it is high, the systemic form should be considered (Fig. 1).[3]

In our cases [*patient 2, 3* (first episode)], Candida spp. appeared as the causative agent of two PHA1 episodes. Candida infections were



Abbreviations: ACTH: Adrenocorticotropic hormone, CAH: congenital adrenal hyperplasia, PHA: Pseudohypoaldosteronism, PRA: Plasma renin activity US: Ultrasonography, UTA: Urinary tract anomaly, 17 OHP: 17 hydroxyprogesterone

Fig. 1. Approach to hyponatremia and hyperkalemia.

the most important causes of clinically proven UTI in our patients, who produced no other uropathogens. Initially, IV antibiotic therapy was started for the patients but there was no reproduction in the first urine culture and IV fluconazole treatment was added to two urine cultures in the presence of the same amount of Candida spp. In our patients, the causes of susceptibility to Candida-related UTIs appeared to be congenital and structural abnormalities of the urinary tract and urinary stasis.[26] It may also be another important risk factor for premature birth history in both patients.[27] Although obstruction and/or urinary tract stones have been identified for renal involvement, the mechanism of settlement and proliferation in the calyx has not been fully elucidated.[28] Further studies are needed on how UTIs due to Candida species lead to secondary PHA1.

These case series show the need for testing for UTIs in afebrile infants with non-specific symptoms such as vomiting and agitation

at admission, and to consider PHA1 as a differential diagnosis when co-existent with hyponatremia and hyperkalemia. Renal US should be performed, especially in male infants when secondary PHA1 is suspected. Obstructive uropathy supports the diagnosis of secondary PHA1. Our patients also demonstrated the transient nature of the aldosterone resistance; therefore, genetic analysis was not performed.

It is controversial in the literature that the most important risk factor leading to aldosterone resistance is UTA or UTI.[29] With younger age, the risk for secondary PHA1 increases, and severe electrolyte imbalance significantly increases in patients with obstructive uropathy.[22] Preterm birth history also facilitates the development of PHA1 by increasing kidney immaturity.[30]

In *patient 1*, UTI, prematurity, and age 3 months were the most important risk factors as the secondary cause of PHA1. *Patient 2* and *patient 3* were found to have UTA, UTI, prematurity, and age under 3 months. *Patient 3* underwent PUV resection surgery in the third month after the first PHA1 attack. However, this patient had PHA1 for the second time after UTI at 4.5 months. The ongoing bilateral grade 3-4 VUR appears to be the cause of the second attack. Possible risk factors for PHA1 in *patient 4* are clear intermittent catheterization, UTI, and age under 3 months. *Patient 5* underwent surgery at the age of 3.5 months due to left UP stenosis. At the age of 6 months, *patient 5* had PHA1 as a consequence of ongoing grade 3-4 HN and UTI. In *patient 6*, UTI was found to be the only secondary cause of PHA1. UTA, UTI, and age less than 3 months in *patient 7* and *patient 8* were possible risk factors.

The management of secondary PHA1 involves sodium supplementation and water replacement, ion exchange resins when there are high potassium values, bicarbonate in some cases, antibiotics for UTIs, and surgical intervention for UTA when necessary.[7] The abnormalities quickly disappear after medical or surgical therapy.[31] The normalization of biochemical tests may be seen within 24 hours.[22] In our study, all patients recovered from their electrolyte imbalances on the third day of hospitalization with antibiotic and/or antifungal treatment for underlying infections and intravenous saline. In *patient 1* and *patient 5*, PRA and aldosterone levels normalized at 2 weeks. Despite the underlying PUV in *patient 2*, PRA and aldosterone post-UTI normalized at 2 weeks. On the other hand, although *patient 8* was given antibiotic treatment for UTI, aldosterone levels did not normalize at 4 weeks. This situation may be related to the ongoing PUV. In the first PHA episode in *patient 3*, PRA and aldosterone levels were normalized at 2 weeks in combination with UTI and PUV, whereas in the second PHA episode caused by UTI alone, the improvement was observed at 4 weeks. Single-dose hydrocortisone and fludrocortisone treatment were given to *patient 1, 6, 7*, and *8* for the possibility of CAH due to poor hemodynamic circulatory findings and biochemical profiles. Glucocorticoid and mineralocorticoid treatment were started without waiting for hormone test results (cortisol, aldosterone, 17 OHP). In the literature, there are cases in which glucocorticoid and mineralocorticoid treatment were initiated and these therapies were discontinued during follow-up.[3,4] In our study, fludrocortisone was discontinued at the end of the first week when the 17 OHP result was normal.

In patients presenting with non-specific symptoms during early infancy, when hyperkalemia and hyponatremia in biochemical parameters are noticed, CAH or adrenal insufficiency and secondary PHA1 should be considered. Urine analysis, urine culture, and renal US imaging are very important in terms of rapid identification, especially in children younger than 3 months or older, up to 8 months. If a pathologic condition is detected in these studies, PHA1 should first come to mind. Fungal infections should not be forgotten in the etiology of UTI because PHA1 episodes can be initiated.

Ethical approval

Ankara University Ethics committee approval for the study was received. (approval number: 14-675-16).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: MB, FG; data collection: FG; analysis and interpretation of results: MB, ZŞ, FG; draft manuscript preparation: ZŞ, FG. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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